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ABSTRACT

Background: The aim of this study is to determine sex differences in long-term outcome after coronary artery bypass grafting (CABG).
Methods: The international randomized controlled IMAGINE study included 2553 consecutive patients with a left ventricular ejection fraction of >40% who underwent isolated CABG. Median follow-up was 32 months (IQR 17–42 months). The composite endpoint comprised of death, myocardial infarction (MI), cerebrovascular event, angina, revascularization and congestive heart failure. Cox regression analysis was used to examine sex differences in outcome post-CABG.
Results: Of the 2553 patients, 2229 were men and 324 (13%) were women. Women were older and more often reported diabetes and hypertension. Smoking and impaired renal function were more prevalent in men. Women experienced a higher event rate during follow-up (composite endpoint 18% vs 12%; P = 0.007). Cox regression showed an increased risk of the composite endpoint in women after adjustment for age (HR 1.48 (95% CI: 1.11–1.97)) which was non-significant after additional adjustment for other confounders (HR 1.26 (95% CI: 0.92–1.72)).
Conclusion: Women have a worse long-term outcome after CABG than men in univariate analysis. However, after adjusting for potential confounders female sex became a non-significant predictor for prognosis, possibly due to the small sample size of women. Definite answers regarding sex-differences in long-term outcome after CABG should come from future pooling of studies comprising a larger number of women.

1. Introduction

Coronary artery disease (CAD) is the main cause of death in women older than 65 years [1]. In 2008 the prevalence of cardiovascular disease in the United States was 35.0% in women compared to 37.4% in men. However age-adjusted mortality rates were higher in women, namely 51.7% versus 48.3% [1]. Previous studies suggest sex differences in treatment and prognosis of CAD, but many discrepancies exist between different studies [2–16]. It remains uncertain whether these differences in outcome are due to a different risk burden between men and women or whether female sex is an independent risk factor of worse outcome and prognosis. Age is a major confounder, as younger, but not older, women have a higher mortality rate than men after myocardial infarction with or without intervention [17–19]. Furthermore, women undergo coronary angiography or percutaneous coronary intervention less often as compared to men [19–21]. The influence of female sex on the outcome after coronary artery bypass grafting (CABG) remains unclear, as previous studies are contradictory

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[2,3,8,13]. In order to determine possible sex differences in long-term outcome after CABG, data from the Ischemia Management with Accupril post-bypass Graft via inhibition of the coNverting Enzyme (IMAGINE) were analysed. IMAGINE is a multicentre, international randomized controlled trial with extensive data concerning baseline characteristics and operational techniques.

2. Methods

2.1. Patient characteristics

The design and the main results of the Ischemia Management with Accupril post-bypass Graft via Inhibition of the coNverting Enzyme (IMAGINE) trial have been previously described in detail [22,23]. In brief, the IMAGINE trial is an international, randomized, double-blind, placebo-controlled, multicentre study that investigated whether early administration of an angiotensin-converting enzyme (ACE) inhibitor after CABG reduced cardiovascular events compared to placebo in stable patients. Patients older than 18 years with a left ventricular ejection fraction (LVEF) of ≥40% who were stable after CABG were included. Exclusion criteria consisted of intolerance or contraindication to ACE inhibitors, insulin-dependent diabetes, concomitant cardiac surgery, serious concomitant disease including severe renal impairment, significant perioperative myocardial infarction, pregnancy and investigational drug use <30 days. The 2553 patients included in this study between 1999 and 2004 were randomly assigned to quinapril 10–20 mg (n = 1280) or to placebo (n = 1273). On average patients were randomized 4 ± 2 days after CABG, with a maximum of 7 days (10 days in France). The primary endpoint was a composite of time to first occurrence of cardiovascular death or resuscitated cardiac arrest, nonfatal myocardial infarction, coronary revascularization, unstable angina, stroke and congestive heart failure that required hospitalization. Five patients were lost to follow-up (0.2%).

For the current analyses all available follow up time was used. The ethics committees of all participating institutions approved the research protocol and all patients gave written informed consent.

2.2. Statistical analysis

Patients were stratified by sex. Baseline categorical variables are presented as percentages (numbers). Differences between sexes were calculated by Chi–Square test. Continuous variables are described as the mean value ± standard deviation (SD) if normally distributed or the median value if the distribution was skewed. Possible differences were tested by *t*-test. All statistical tests were two-sided using $p < 0.05$ as level of significance. The primary endpoint was evaluated using a Cox proportional hazard model where men served as the reference category. Results are expressed as hazard ratios (HR) with 95% confidence intervals (95% CI). To identify possible confounders all baseline characteristics and surgical characteristics were related to the composite endpoint separately, adjusted for age. Correlation with the determinant sex was evaluated by a Pearson's correlation chi-square in variables that were significantly associated with the composite endpoint. Those with a p-value <0.1 at Pearson's correlation chi-square, as well as age and sex, were added in the multivariate model. Since previous studies demonstrated that body surface area (BSA) is associated with a worse outcome post-CABG in female sex we used BSA instead of body mass index [13,14]. Because of the well-documented surgical characteristics, a subanalysis was made regarding the type of grafts used during CABG. All statistical analyses were performed using SPSS Version 21.0.

3. Results

3.1. Patient characteristics

Out of the 2553 included patients 324 (13%) were women. Median follow-up was 32 months in both men and women (IQR 17–42 in men, IQR 15–42 in women). Baseline characteristics are shown in Table 1. Women were on average 5 years older than men and more often reported hypertension and a family history of CAD. Men more often smoked and revealed decreased renal function (all $P < 0.01$).

3.2. Characteristics of CABG

On average men received more grafts (3.3 versus 3.0 in women; $P < 0.01$) (see Table 2). The percentage of off-pump CABG compared to CABG on cardiopulmonary bypass did not differ between men and women (18% versus 21%, $P = 0.19$). Furthermore, there was no difference in complete revascularization, defined as all vessels >1 mm with a stenosis >70% having been bypassed, between women and men ($P = 0.21$).

3.3. Endpoint

Women were more likely to experience the composite endpoint, 18% versus 12% in men ($P < 0.01$), as shown in Table 3. This difference is mainly driven by the distribution of unstable angina (5% in women vs 1.9% in men), coronary revascularization (1.2% in women vs 0.4% in men) and congestive heart failure (2.5% in women vs 0.9% in men).

Table 1
Baseline characteristics.

	Men (n = 2229)	Women (n = 324)	*P*-value
Age, years (SD)	60 ± 10	65 ± 10	<0.01
Median follow-up in months (IQR)	32 (17–42)	32 (15–42)	0.21
Medical history			
Myocardial infarction	40 (887)	35 (114)	0.11
CABG	3 (58)	2 (6)	0.42
Percutaneous coronary intervention	17 (388)	21 (67)	0.15
Peripheral vascular disease	7 (151)	9 (30)	0.10
Stroke/TIA	1 (33)	1 (4)	0.73
Cardiovascular risk factors			
LDL cholesterol (mmol/L) (SD)	2.9 ± 1	2.9 ± 1	0.95
Diabetes	10 (212)	13 (41)	0.08
HbA1c (mmol/mol) (SD)	39 ± 8	41 ± 32	<0.01
Systolic blood pressure (mmHg) (SD)	121 ± 14	124 ± 15	0.11
Current or former smoker	74 (1658)	52 (167)	<0.01
Family history of coronary artery disease	67 (1480)	73 (235)	0.03
Body surface area (m^2) (SD)	2.0 ± 0.2	1.8 ± 0.2	<0.01
Heart rate (bpm) (SD)	82 ± 13	81 ± 12	0.23
Left ventricular ejection fraction (%) (SD)	60 ± 7	61 ± 10	0.43
MDRD (estimated GFR based on creatinine) (SD)	63 ± 15	108 ± 32	<0.01
Medication			
Acetylsalicylic acid (ASA)	74 (1567)	72 (205)	0.44
Betablockers	78 (1657)	79 (224)	0.92
Calcium-channel blockers	767 (36)	107 (38)	0.67
Diuretics	9 (184)	9 (25)	0.97
ACE inhibitors	21 (433)	19 (54)	0.55
Statins	65 (1384)	60 (172)	0.09

Continuous variables are presented as mean ± SD; categorical variables are presented as percentages (*n*)SD, standard deviation; IQR, inter quartile range; LDL, low-density lipoprotein; MDRD, modification of diet in renal disease; GFR, glomerular filtration rate.

Table 2
Surgical characteristics.

Patient characteristics % (n)	Men (n = 2229)	Women (n = 324)	*P*-value
Off-pump CABG	18 (407)	21 (69)	0.19
Number of grafts	3.3 ± 1.1	3.0 ± 1.1	<0.01
Use of LIMA	95 (2120)	92 (297)	0.01
Use of RIMA	19 (415)	9 (28)	<0.01
Use of free IMA	3 (61)	6 (18)	<0.01
Use of other arterial grafts	20 (445)	10 (31)	<0.01
Use of saphenous vein	79 (1757)	79 (257)	0.84
Endarterectomy	6 (111)	8 (22)	0.21
Complete revascularization	88 (1962)	90 (293)	0.21

Continuous variables are presented as mean ± SD; categorical variables are presented as percentages (*n*).
CABG, coronary artery bypass grafting; Free artery bypass, composite of radial artery, all other arteries than LIMA or RIMA; IMA, internal mammary artery; LIMA, left internal mammary artery; mixed grafts, arterial or venous grafts; RIMA, right internal mammary artery.

Cox regression analysis demonstrated an increased risk of the composite endpoint in women compared to men after adjustment for age with an HR of 1.48 (95%CI 1.11–1.97). Seven other variables were after adjustment for age associated with the composite endpoint, family history of CAD (HR 1.36 (95%CI: 1.06–1.74)), a medical history of PCI (HR 1.65 (95%CI: 1.28–2.11)), CABG (HR 2.28 (95%CI: 1.39–3.72)) or peripheral vascular disease (HR 1.80 (95%CI: 1.30–2.51)), BSA (HR 0.61 (95%CI: 0.38–0.98)), complete revascularization (HR 0.63 (95%CI: 0.48–0.85)) and number of grafts used (HR 0.78 (95%CI 0.71–0.87)). Of these seven variables only a family history of CAD (P = 0.03), number of grafts (P < 0.01) and BSA (P < 0.01) correlated with sex and were added to the multivariate model (Fig. 1). Female sex was not associated with the composite endpoint in the multivariate analysis (HR 1.26 (95%CI: 0.92–1.72), Fig. 1) nor was BSA (HR 0.74 (95%CI: 0.45–1.23). A family history of CAD remained associated with the composite endpoint (HR 1.35 (95%CI: 1.05–1.73)) as well as number of grafts used (HR 0.79 (95% CI: 0.72–0.88)).

In the original IMAGINE trial, there were no differences in the incidence of the primary endpoint between the quinapril and placebo group after subdividing by sex.

4. Discussion

The current study demonstrates that women have an increased risk of an adverse outcome after CABG compared to men during 2.5 years of follow-up. However, in the multivariate analysis female sex is not an independent predictor for developing the composite endpoint in this cohort potentially due to lack of power. At baseline

Table 3
Composite endpoint.

Patient characteristics	Men (n = 2229)	Women (n = 324)	*P*-value
Composite endpoint	12 (273)	18 (57)	<0.01
Cardiovascular death	0.8 (17)	1.2 (4)	
Myocardial infarction (non-fatal)	1 (22)	1.2 (4)	
Documented angina (not req. hosp.)	6.1 (137)	6.2 (20)	
Unstable angina (req. hosp.)	1.9 (43)	5 (15)	
Coronary revascularization	0.4 (9)	1.2 (4)	
Stroke	1.0 (23)	0.3 (1)	
Resuscitation or cardiac arrest	0.1 (2)	0.3 (1)	
Congestive heart failure (req. hosp.)	0.9 (20)	2.5 (8)	

Categorical variables are presented as percentages (*n*).
MDRD, estimated GFR based on creatinine; Req. hosp., requiring hospitalization; TIA, transient ischemic attack.

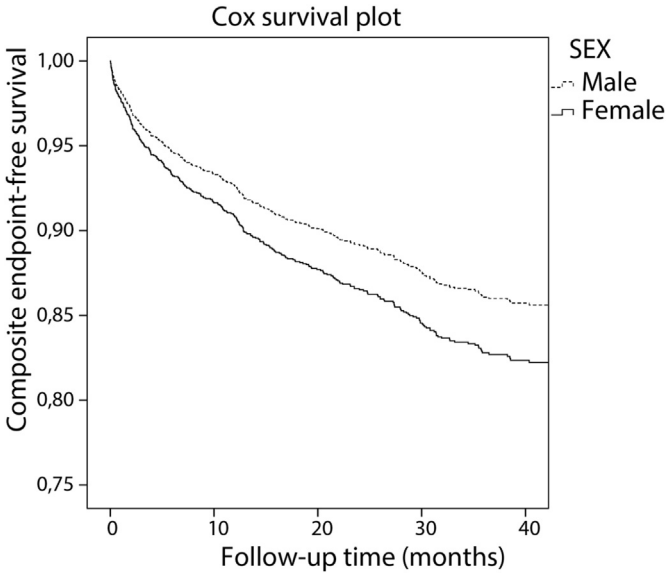

Fig. 1. Cox survival plot. Cox survival plot for composite endpoints in women and men.

women were older and more often had hypertension, a family history of CAD and a smaller BSA. On the other hand men smoked more often and had more frequently renal dysfunction. In regard to other studies both men and women included in the IMAGINE trial reported a relatively low burden of cardiovascular risk factors. Interestingly, our results showed no differences in percentage of off-pump CABG between men and women and no benefit of off-pump CABG for the composite endpoint in both men and women. Previous studies showed an increased risk of adverse outcome in women for CABG on cardiopulmonary bypass, compared to off-pump CABG [4–8,10,14]. The majority of prior studies included emergency CABGs whereas we excluded these unstable patients, which makes it difficult to directly compare results [4–8,10–15]. Furthermore, we used a composite endpoint where others used death as primary outcome. Some studies showed an increased risk in women for early mortality [2,8,10], but the majority found no sex differences [3,4,12–15]. Others only found an increased risk for mortality in women after CABG on cardiopulmonary bypass and not after off-pump CABG [5–7,11,16]. The higher risk in women we found in the univariate analysis is caused primarily by a higher rate of unstable angina and coronary revascularization as the number of deaths was equal in both sexes. This is consistent with the finding in this study that the number of grafts used is significant between women and men in the multivariate analysis. The difference in univariate analysis between women and men could therefore point towards a difference in coronary artery diameter: as women are smaller, they have smaller coronary arteries that are technically more demanding in CABG. Indeed, BSA was a confounding factor in this study.

5. Limitations

Main limitation of this study is the small sample size of women. Women comprised only 13% of our study population compared to 24% on average in other studies [2–8,10–16]. Unfortunately no screenings log, with numbers screened patients and the reason of exclusion, is available so the low inclusion rate in women remains elusive. One of the possible explanations is the exclusion of patients with severe comorbidities, as women are known to be more severely impaired. The sample size of women introduces an unexpected power problem in the multivariate model, where sex does not seem to associate with the composite endpoint whereas the cox

survival plot shows a difference between women and men.

Our results are only applicable to stable patients undergoing CABG since unstable patients were excluded from the study, just as patients with a clinical need for ACE-inhibitors (e.g. severe renal insufficiency and insulin dependent diabetes). We are to our knowledge the first study to include only stable patients and since a large part of the CABG population is stable before surgery, it is relevant to investigate sex differences in outcome in this subpopulation. It could be that sex differences are still present in the unstable group.

Echocardiography testing for diastolic dysfunction which may eventually evolve in to heart failure with preserved ejection fraction (HFpEF) was not performed. As diastolic dysfunction is common in the general population [24] more prevalent among women undergoing cardiac surgery [25] and associated with worse outcome in CAD patients [26], this could be a confounding factor. Also, no data were available on relief of angina symptoms, one of the indications for CABG surgery. However, we do not think this affected the results, since persisting angina was well-documented.

The difference between women and men found in this study was mainly due to differences in 'soft' endpoints such as unstable angina and cardiac revascularization, rather than more robust endpoints such as death. As these 'soft' endpoints are more prone to misclassification, this could potentially have induced non-differential (more in women) misclassification of the outcome. Unfortunately, this type of bias is difficult to overcome and may have overestimated the sex difference.

The duration of follow-up was limited to 2.5 years. Although the majority of the present studies had a limited follow-up of 30 days after CABG [2,4,6,7,10–15], some have shown a decrease in the sex gap after long-term follow-up [3,27], as described earlier by M Claassen et al. [28]. Future studies should examine a larger number of women during long-term follow-up. For example, an individual participant data analysis of current studies could improve the power to detect sex-specific differences and their determinants in outcome between women and men after CABG.

6. Conclusion

Women have a worse long-term outcome after CABG than men in univariate analysis. However, after adjusting for potential confounders female sex became a non-significant predictor for prognosis, possibly due to the small sample size of women. Definite answers regarding sex-differences in long-term outcome after CABG should come from future pooling of studies comprising a larger number of women.

Conflict of interests

None.

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